
بسم الله الرحمن الرحیم

IgA Nephropathy

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INTRODUCTION

- Immunoglobulin **A (IgA) nephropathy is the most common lesion found to cause primary glomerulonephritis** through out most developed countries of the world .

- IgA deposits may also be seen on kidney biopsy in individuals with no evidence of renal disease .

- The reported incidence of mesangial IgA deposition in apparently healthy individuals ranges from **3 to 16 percent** These cases had no clinical features of nephritis, but their renal biopsy was consistent with IgA nephropathy.

INTRODUCTION

- There is a large cohort of undiagnosed "latent" IgA nephropathy in the general population.

- The process of mesangial IgA deposition is likely to be separate from the induction of glomerular injury

- IgA deposition does not necessarily need to be followed by nephritis.

INTRODUCTION

- There are also a number of reports documenting IgA deposition in other forms of glomerulonephritis.
- These particularly include :
  - thin basement membrane nephropathy
  - lupus nephritis
  - minimal change disease
  - diabetic nephropathy.

INTRODUCTION

- Immunoglobulin A (IgA) nephropathy (IgAN) is a heterogeneous disease with a highly variable risk of disease progression to end stage renal disease (ESRD) after 10 years **varying between<10% and 60% .**

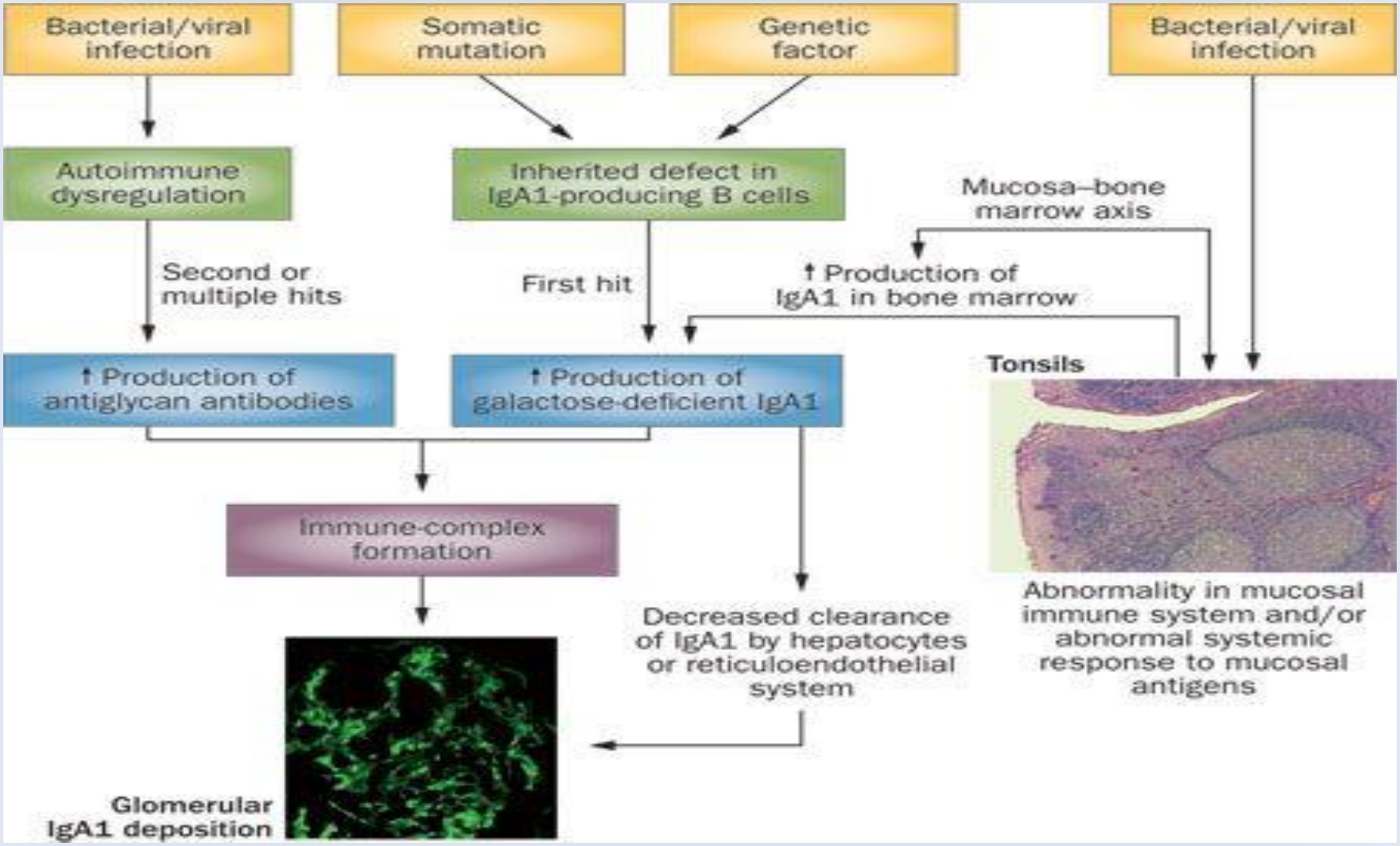
- As a result, it is challenging to accurately identify individual patients at high risk of disease progression.

INTRODUCTION

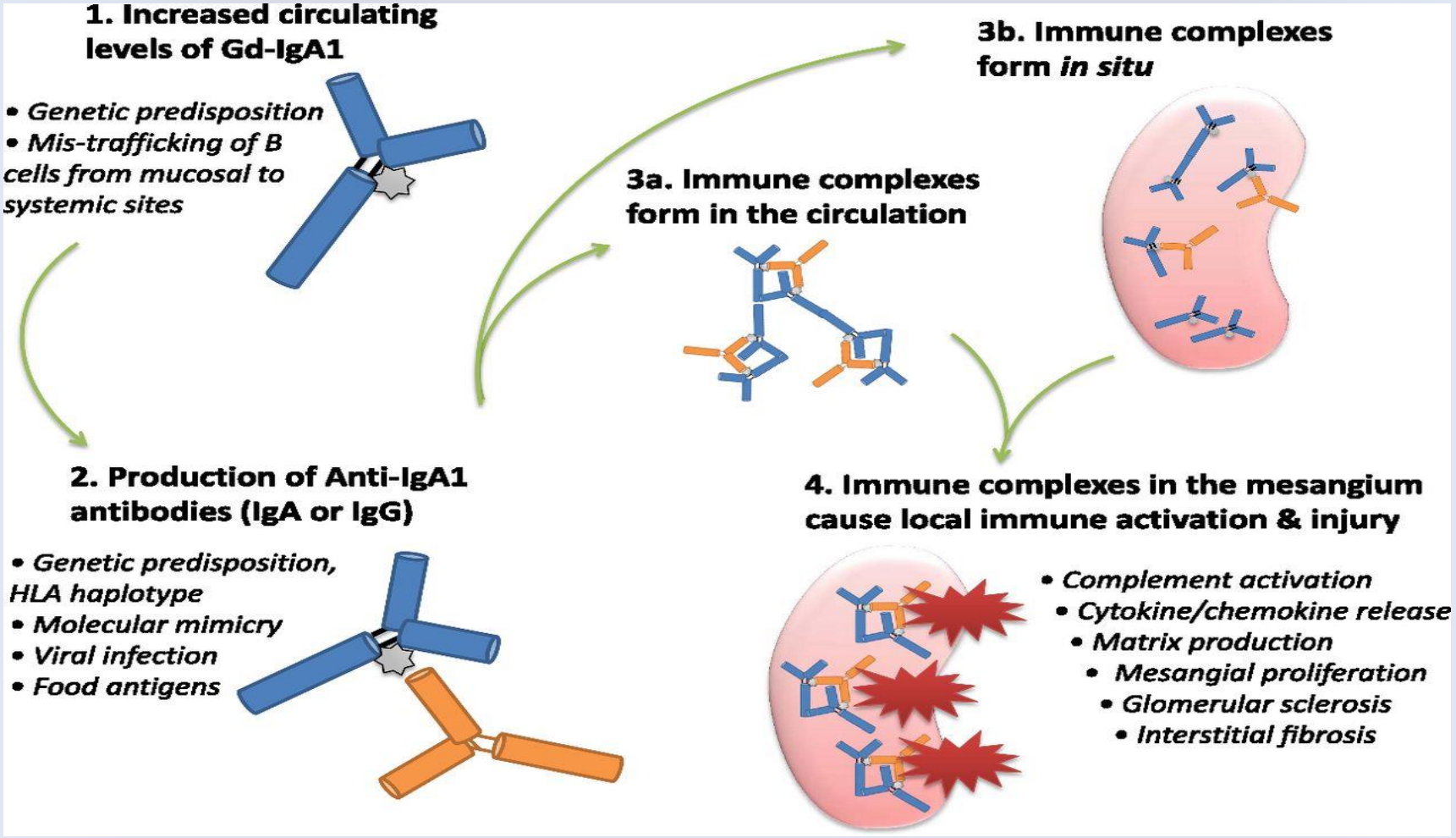
- Familial clustering, ethnic differences, and regional discrepancies suggest a genetic component to IgAN.

- Genome-wide association studies (GWASs) have identified several susceptibility genes and loci that have been associated with IgA N, including pathways involving :
  - the major histocompatibility complex
  - complement system
  - mucosal innate immunity
  - mucosal IgA production regulation.

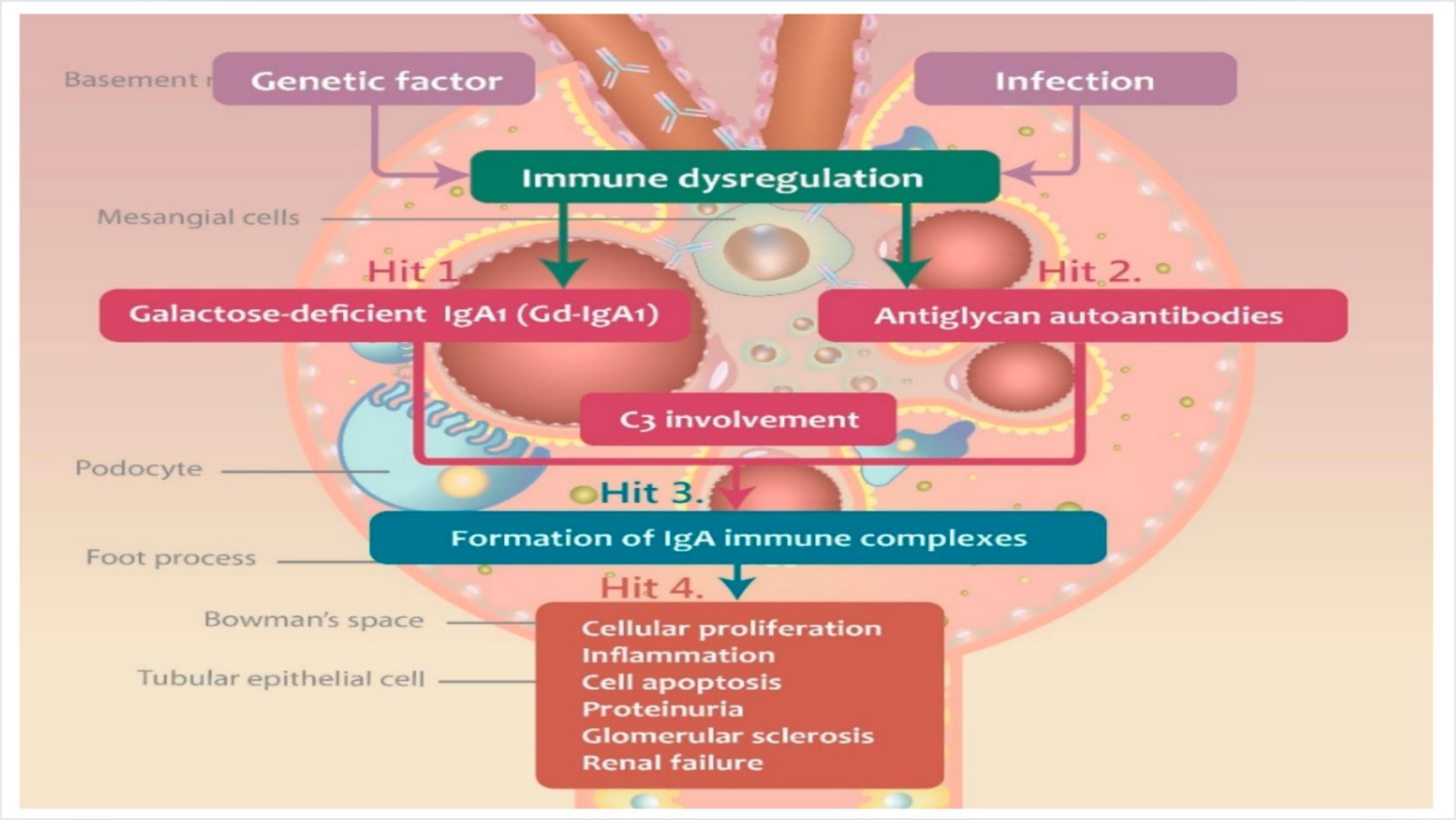
Pathogenesis



Pathogenesis



Pathogenesis



Pathogenesis

- Upstream factors determining synthesis of Gd-IgA1 are likely to involve an abnormal mucosal immune response, driven by either dysregulated immune regulation within the **mucosal-associated lymphoid tissue(MALT**) or dysbiosis of the normal mucosal microbiota.

- It is probable that genetic factors contribute variably to many elements of this paradigm, although their relative contribution is likely to vary from patient to patient and population to population

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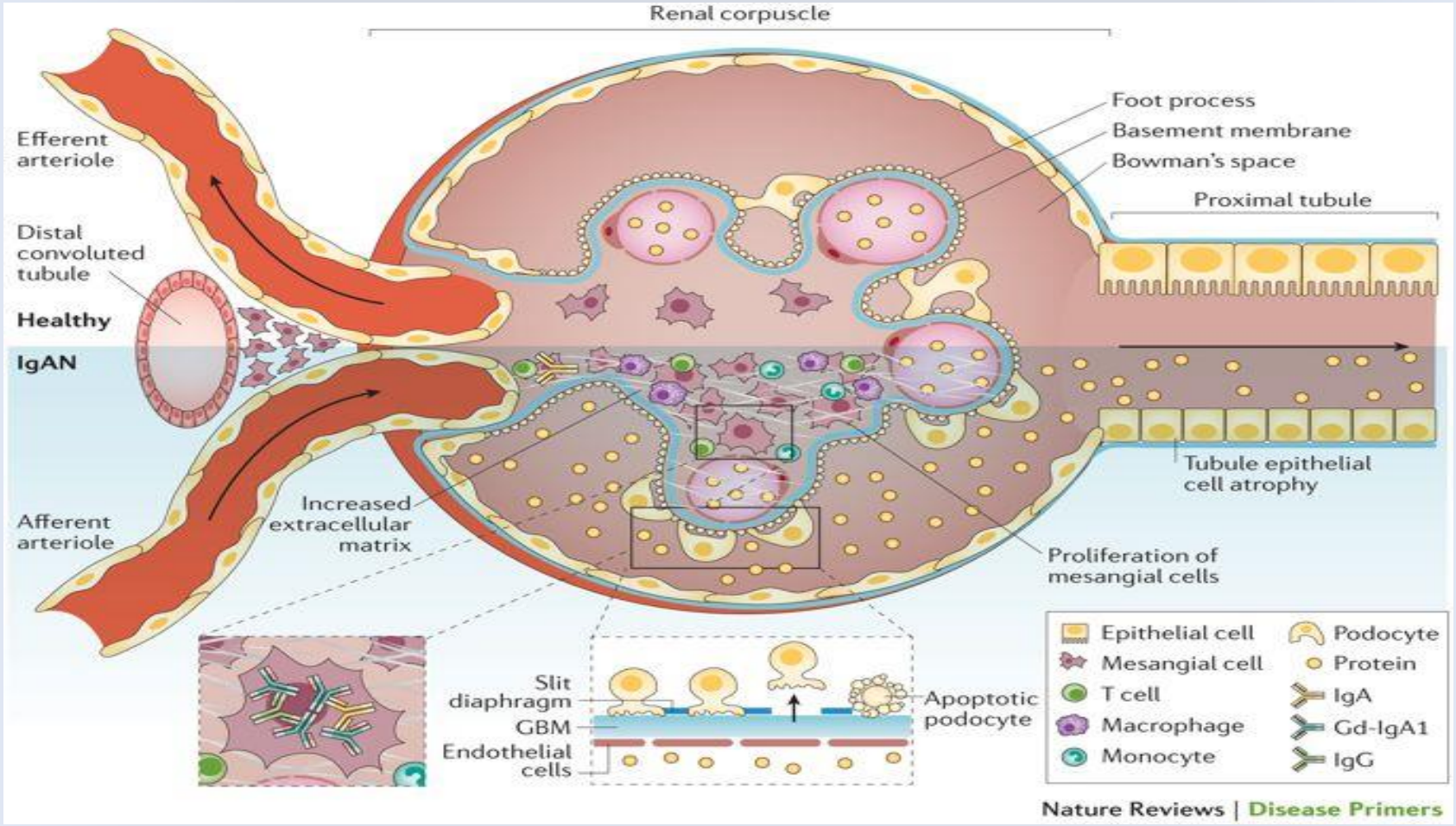
Pathogenesis



Pathogenesis

- **Mucosal infections** may be associated with **episodes of visible hematuria and an increase in circulating IgA immune complex levels in IgAN.**

- Systemic IgA responses to mucosal antigen challenge are exaggerated in IgAN and many of the features of mesangial IgA are those typically associated with IgA produced in the mucosal lymphoid tissue.

- Mucosal IgA , unlike systemic IgA, is typically polymeric, of low affinity, and relatively poorly O-galactosylated , the physicochemical characteristics typically observed in serum and glomeruli in IgAN.

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Pathogenesis

- **The gut–kidney axis in IgA nephropathy**
- **gut-associated lymphoid tissue plays a major role in the development of IgA nephropathy.**
- Experimental models have demonstrated the development of IgA nephropathy in mice producing high levels of IgA and **overexpressing BAFF, a B-cell factor crucial for IgA synthesis**
- There is some evidence that this mechanism may operate in humans since increased levels of BAFF and APRIL have been detected in a subset of patients with IgA nephropathy .

Pathogenesis

- GWAS in IgAN have identified susceptibility loci in genes that are directly associated with intestinal mucosal immunity.

- The **gut microbiome exerts a direct regulatory effect** on the MALT .

- The role of intestinal microbiota in patients with IgA nephropathy was recently investigated.

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Pathogenesis

- Much more work is required to better understand the complex relationship between the microbiota and IgA synthesis by the MALT in IgAN and whether **interference with the gut microbiome might be a therapeutic avenue in IgAN.**

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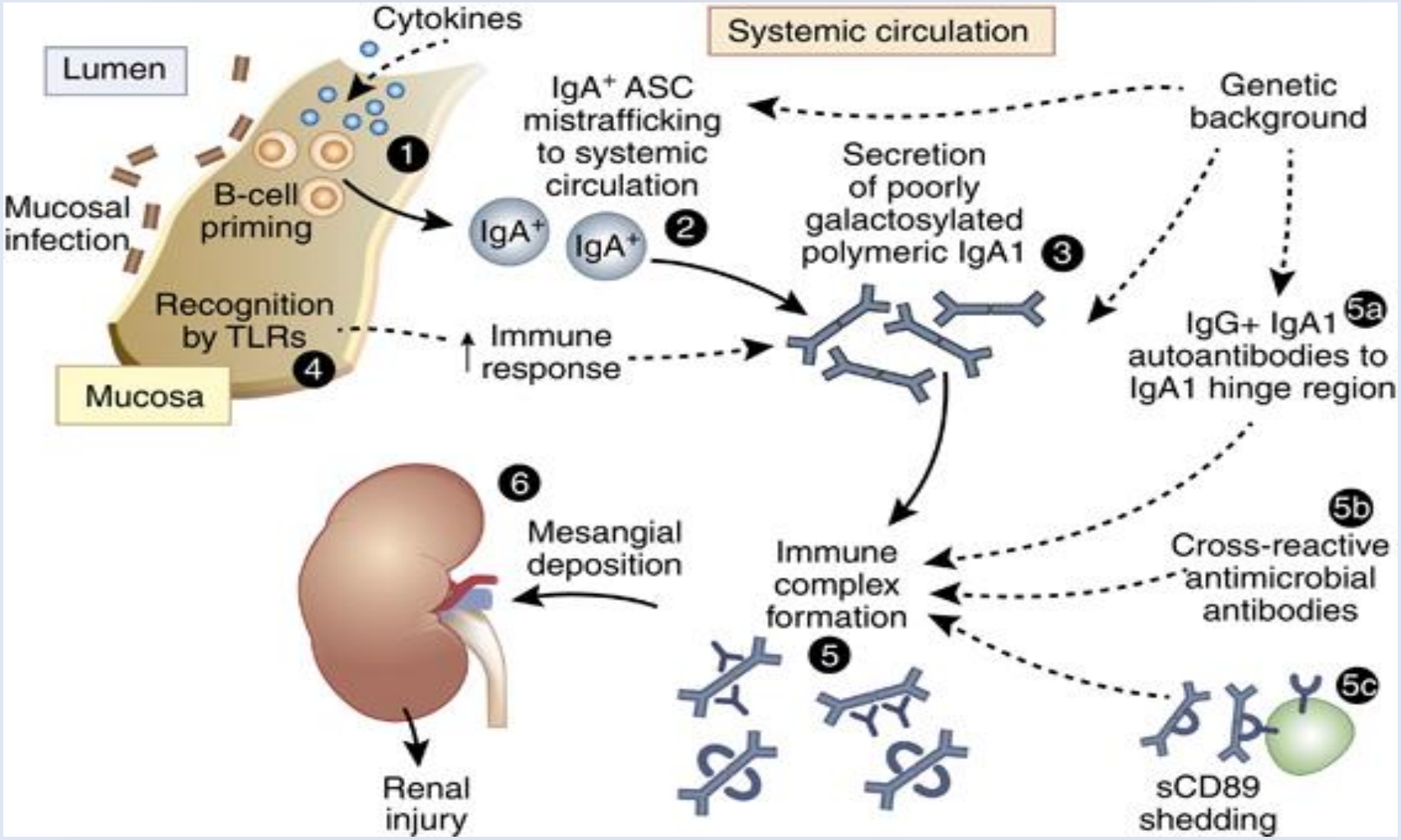
Cytokines
Systemic circulation
Lumen
IgA+ ASC mistrafficking to systemic circulation
Genetic background
Mucosal infection
B-cell priming
1
IgA+
IgA+
2
Secretion of poorly galactosylated polymeric IgA1
3
Recognition by TLRs
4
Immune response
IgG+ IgA1 autoantibodies to IgA1 hinge region
5a
Mucosa
6
Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
5
5c
Renal injury
sCD89 shedding

Pathogenesis

- In a study that examined the **miRNA** profile of 75 patients with IgA nephropathy and 75 healthy controls ,the following findings were observed:

- Leukocytes from patients with IgA nephropathy **overexpressed a specific miRNA (miR-148b)**

- The **upregulation of miR-0148b** was also associated with Gd-IgA1.

Pathogenesis

- **IgA-induced activation of mesangial cells** :
- Polymeric IgA elicits a phenotypic transformation in mesangial cells in vitro, with mesangial cell proliferation and secretion of extracellular matrix components .
- **There is increased expression** :
  - TGF-beta
  - Renin-angiotensin
  - IL-6
  - Platelet-derived growth factor (PDGF) B and D chains

Pathogenesis

- **Mesangial cell-podocyte crosstalk** :
- **loss of podocyte markers** (nephrin, ezrin, and podocin) influence of mesangial cell-derived soluble mediators (such as tumor necrosis factor [TNF]-alpha and TGF-beta)

- podocytopathic variant of IgA nephropathy in which podocyte injury is the principle feature, possibly due to a direct interaction between IgA immune complexes and podocytes .

CLINICAL RISK FACTORS

- clinical risk factors and renal outcome in IgAN:
  - eGFR
  - Proteinuria
  - Blood pressure
  - Sex
  - Race
  - BMI
  - Hematuria

HISTOLOGIC RISK FACTORS

- MEST-C histologic scoring system:
  - mesangial hypercellularity
  - endocapillary hypercelluarity
  - segmental sclerosis
  - interstitial fibrosis
  - tubular atrophy
  - cellular or fibrocellular crescents
  - C4d staining

Schimpf *et al. BMC Nephrology* (2018) 19:328
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BMC Nephrology

RESEARCH ARTICLE Open Access

Renal outcomes of STOP-IgAN trial patients in relation to baseline histology (MEST-C scores)

Judith Isabel Schimpf[1†], Till Klein[1,2†], Christina Fitzner[3], Frank Eitner[4], Stefan Porubsky[5,6], Ralf-Dieter Hilgers[3], Jürgen Floege[1], Hermann-Josef Groene[5] and Thomas Rauen[1*]

Abstract

Background: The Oxford classification of IgA nephropathy (IgAN) defines histologic criteria (MEST-C) that provide prognostic information based on the kidney biopsy. There are few data on the predictive impact of this classification in randomized clinical trial settings.

Methods: We performed an exploratory analysis of MEST-C scores in 70 available renal biopsies from 162 randomized STOP-IgAN trial participants and correlated the results with clinical outcomes. Analyses were performed by researchers blinded to the clinical outcome of the patients. Biopsies had been obtained 6.5 to 95 (median 9.4) months prior to randomization.

Results: Mesangial hypercellularity (M1) associated with higher annual eGFR-loss during the 3-year trial (M1: − 5.06 ± 5.17 ml/min/1.73 m^2, M0: − 0.79 ± 4.50 ml/min/1.73 m^2, $p = 0.002$). An M0-score additionally showed a weak association with full clinical remission, whereas the percentage of patients losing ≥15 ml/min/1.73 m^2 over the 3-year trial phase was higher among those scored as M1. Among patients with additional immunosuppression, ESRD occurred more frequently in patients when tubulointerstitial fibrosis (T1/2) was present (T1/2 = 33%, T0 = 0%, $p = 0.008$). In patients receiving supportive care only, ESRD frequencies were similar (T1/2 = 18%, T0 = 7%, $p = 0.603$). At randomization, eGFR was significantly lower when tubulointerstitial fibrosis was present (T1/2: 45.2 ± 15.7 ml/min/1.73 m^2, T0: 74.6 ± 28.2 ml/min/1.73 m^2, $p < 0.0001$). Endocapillary hypercellularity (E), and glomerular segmental sclerosis (S) were not associated with any clinical outcome parameter. In the analyzed cohort, patients with glomerular crescents (C1/2 scores) in their biopsies were more likely to develop ESRD during the 3-year trial phase, but this trend was only significant in patients under supportive care.

Conclusions: This secondary analysis of STOP-IgAN biopsies indicates that M1, T1/2 and C1/2 scores associate with worse renal outcomes.

Keywords: IgA nephropathy, IgAN, MEST-C, Oxford classification, STOP-IgAN

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Original Paper

Prediction of ESRD in IgA Nephropathy Patients from an Asian Cohort: A Random Forest Model

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Ming Xia[a] Guochun Chen[a] Liyu He[a] Letian Zhou[a] Xuejing Zhu[a]
Hong Liu[a]

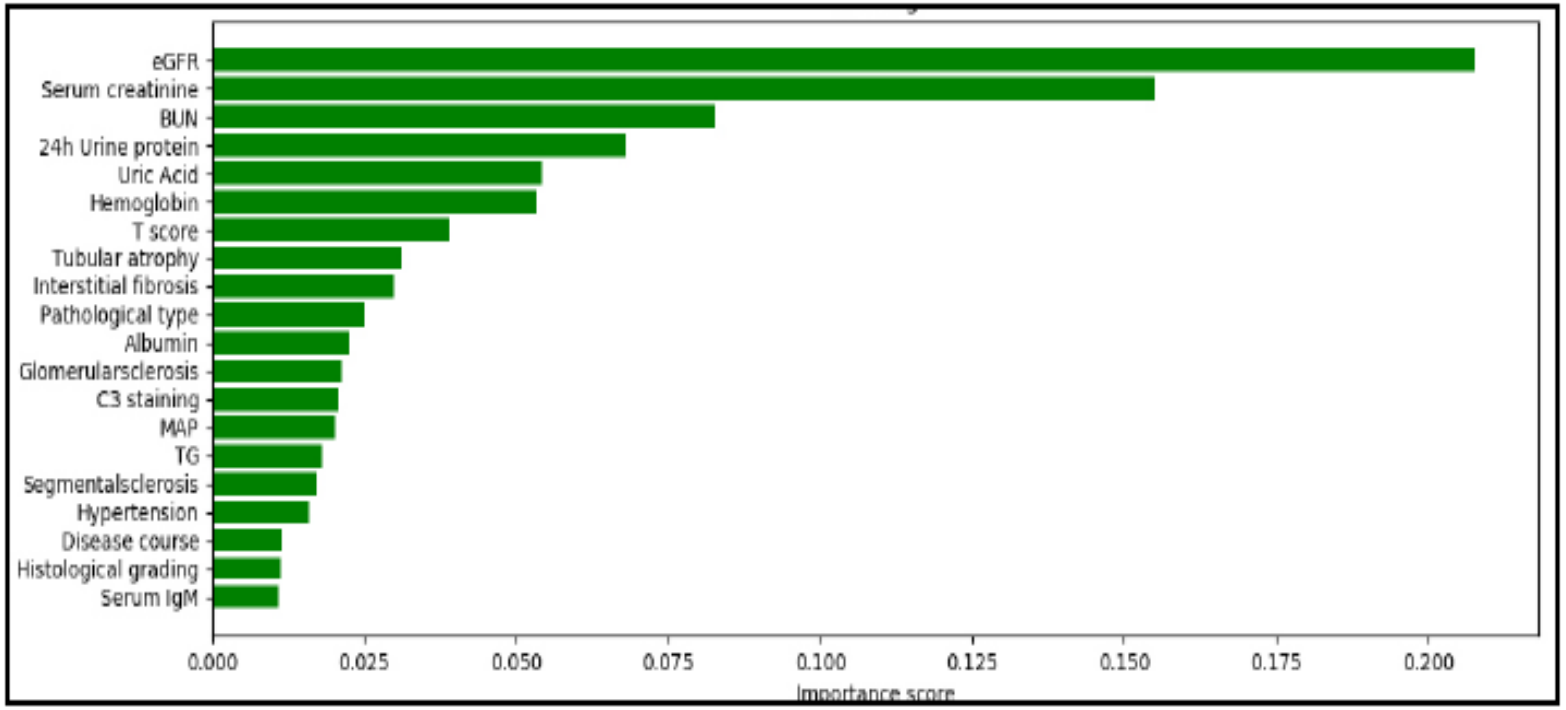
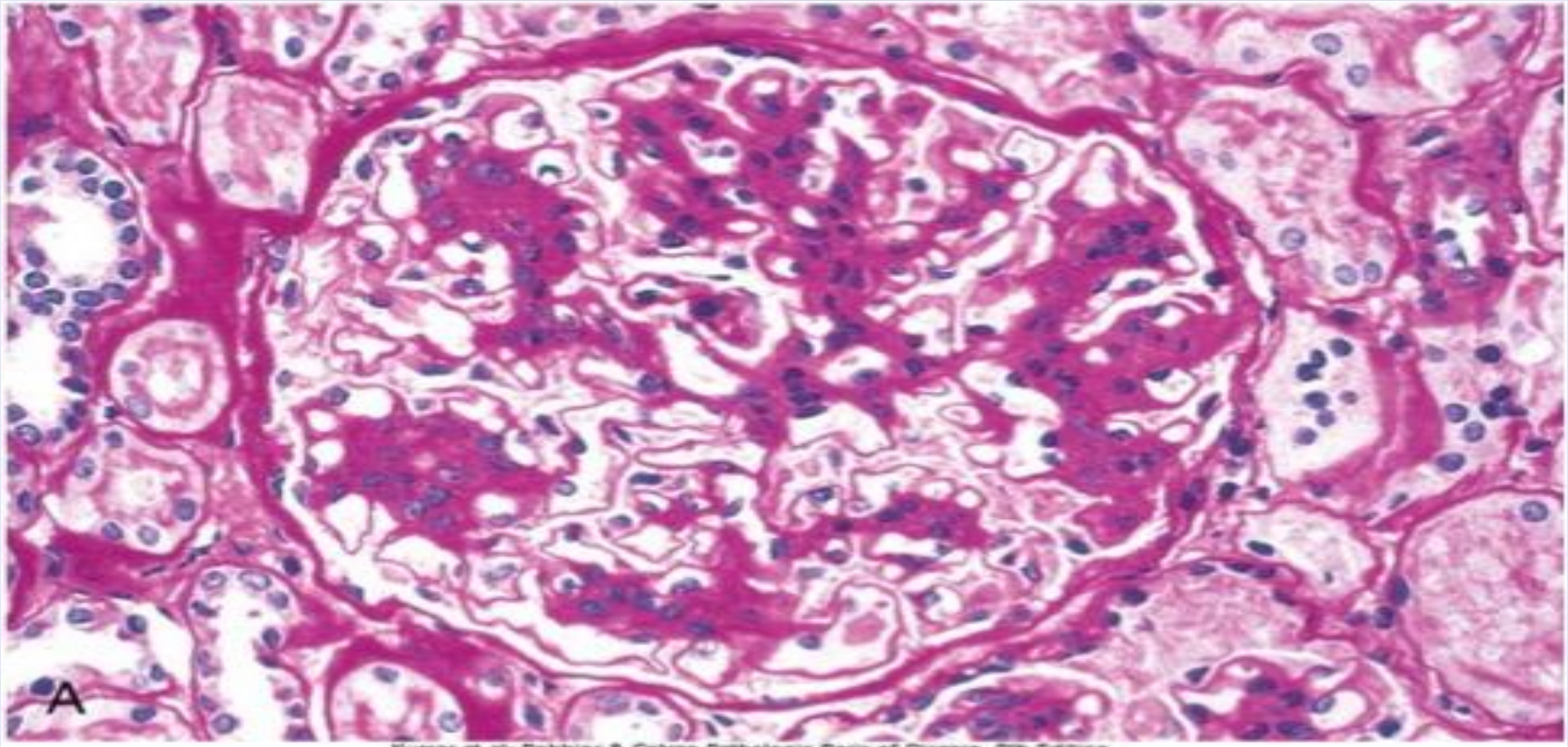


Fig. 3. Contribution of predictors of ESRD in IgAN patients (Top 20 displayed) eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen,TG: Triglyceride.

Table 1 | **MEST-C criteria in the updated Oxford Classification of IgA Nephropathy**[3]

Histological variable	Definition	Score
Mesangial hypercellularity	More than four mesangial cells in any mesangial area of a glomerulus	• M0: <50% of glomeruli showing mesangial hypercellularity • M1: >50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	Hypercellularity due to an increased number of cells within glomerular capillary lumina	• E0: no endocapillary hypercellularity • E1: any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis	Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft	• S0: absent • S1: present in any glomeruli
Tubular atrophy/ interstitial fibrosis	Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater	• T0: 0–25% of cortical area • T1: 26–50% of cortical area • T2: >50% of cortical area
Cellular or fibrocellular crescents	Percentage of glomeruli with cellular or fibrocellular crescents	• C0: absent • C1: 0–25% of glomeruli • C2: ≥25% of glomeruli

M, mesangial hypercellularity; C, crescents; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis. Modified with permission from Macmillan Publishers Limited © Roberts, I. S. D. *Nat. Rev. Neph.* **8**, 445–454 (2014).



IgA nephropathy. **A,** Light microscopy showing mesangial proliferation and matrix increase. **B,** Characteristic deposition of IgA, principally in mesangial regions, detected by immunofluorescence.

LIGHT MICROSCOPY IMAGE

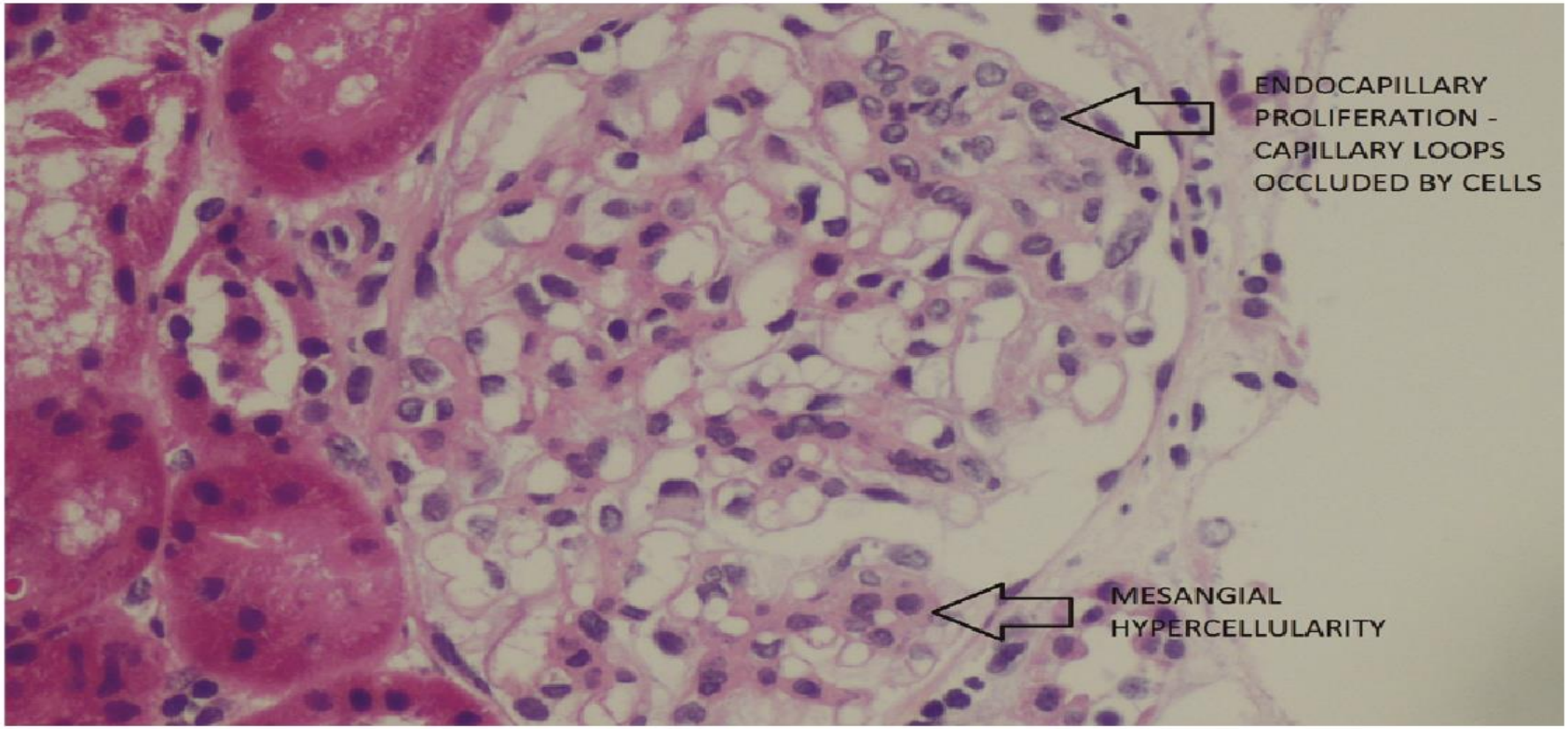
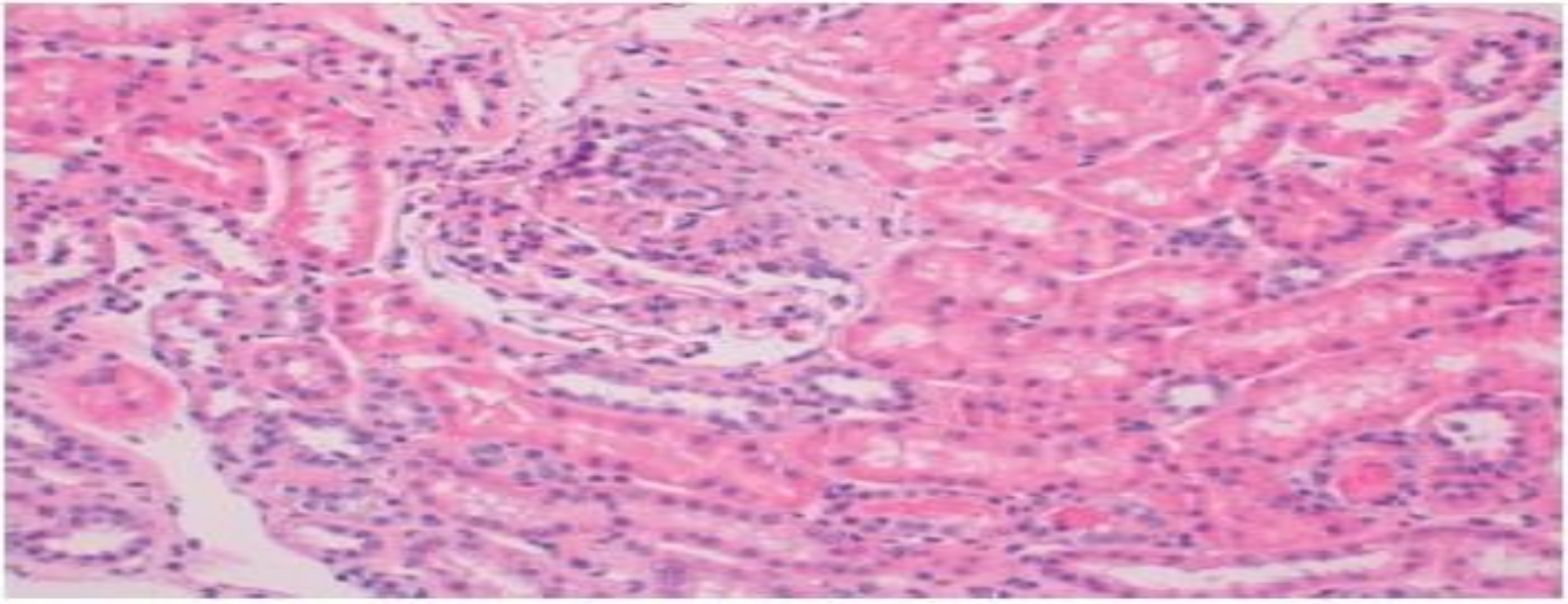
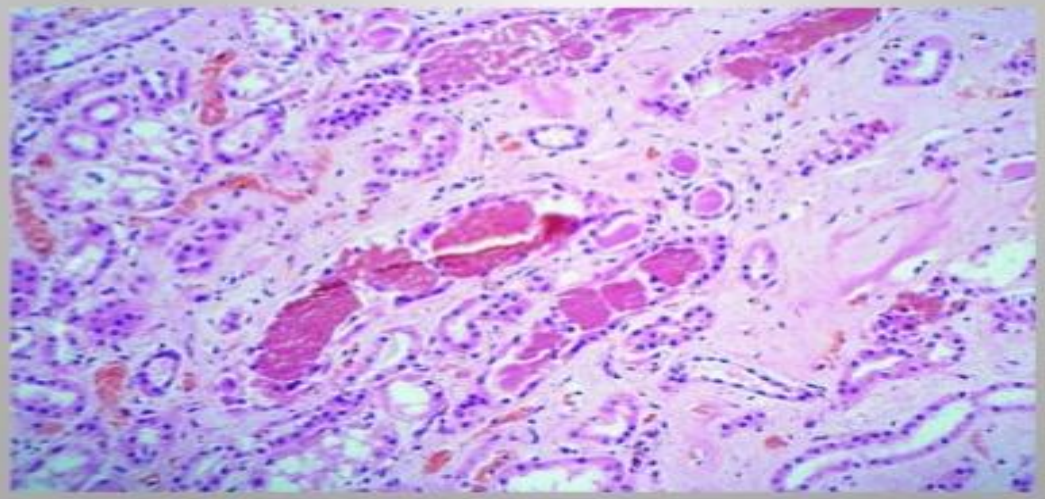


Figure 2: Features of mesangial hypercellularity and segmental endocapillary proliferation marked by block arrows

Figure 1

Kidney biopsy. Hematoxylin and eosin stain with 20x amplification. Cellular crescent occupying 25% of circumference of the glomerulus. Interstitium and tubules are preserved.





Acute kidney injury in IgA nephropathy. Tubular occlusion by red blood cells. This appearance may be associated with only minor glomerular changes.

BIOMARKER RISK FACTORS

- A number of putative IgAN-specific biomarkers were discussed, including :
- serum levels
  - Gd-IgA1
  - Gd-IgA1–specific autoantibodies
  - IgA-IgG immune complexes
- Urinary levels
  - Gd-IgA1
  - CD89
  - CD71
- podocyte urokinase - type plasminogen activator receptor.

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Treatment

- The basis for effective management of IgAN :
- ACEi or ARB
- Adequate blood pressure control
- A low-sodium intake diet
- Aerobic physical exercise
- Adequate loss of weight
- Tobacco avoidance

Treatment
STOP trial

- **STOP-IgAN** trial randomized patients to :
  - supportive treatment
  - steroids alone
  - steroids in conjunction with sequential cyclophosphamide and azathioprine based on eGFR.
- Immunosuppression transiently reduced proteinuria over 3 years but had no impact on eGFR and only resulted in significant, particularly , infectious adverse events.
- Proteinuria reduction occurred mostly in the steroid and not immunosuppressive combination therapy group.

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Treatment
TESTING trial

- **TESTING trial** randomized patients to 6 months :
  - steroids
  - placebo
- **There was a significant reduction in the risk of a 40% decline in eGFR or ESKD in the steroid group.**

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Treatment
VALIGA study

- **mesangial hypercellularity is a risk factor for progression and may be reversed by steroid therapy**.
- prednisone and azathioprine therapy in addition to anticoagulant and antiplatelet treatment
- anticoagulation and anti-platelet therapy only
- Ten years after the end of the treatment the renal **survival was significantly better in children previously treated with corticosteroids/immunosuppressors**

Néphrologie & Thérapeutique 14 (2018) S13–S21

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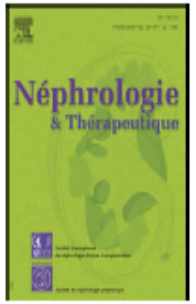

IgA

Treatment of IgA nephropathy: Recent advances and prospects

Rosanna Coppo

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Treatment
NEFIGAN trial

- **NEFIGAN trial** randomized controlled trial was double blinded and placebo controlled and included 6-month run-in, 9-month treatment and 3-month follow-up.
- Targeted-release formulation of budesonide (16 mg/d; 8 mg/d)
- placebo
- mean urine protein–creatinine ratio decreased 32% from baseline at 12 months versus an increase of 0.5% for placebo.
- At 9 months, estimated glomerular filtration rate stabilized with targeted-release formulation of budesonide but decreased 9.8% with placebo (targeted-release formulation of budesonide versus placebo: $P < 0.001$).
- No increase in serious adverse events and particularly infections were reported in treated patients.

Treatment

- Although previous studies suggested mycophenolate mofetil (MMF) was not effective for treatment of IgAN, 2 recent trials add conflicting information.
- A mostly **Caucasian trial** was stopped early for futility because there was **no MMF effect** on the proteinuria-based primary outcome.
- **Chinese trial** randomized patients to 6 months:
  - full dose steroids or
  - lower dose steroids with MMF.
- **After 1 year, complete proteinuria remission was similar between the 2 groups, but with fewer steroid-related adverse events in those treated with MMF.**
- **This study reintroduces the possibility that MMF may be effective for IgAN**.

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Treatment

- Tonsillectomy remains a controversial therapy for IgAN .
- A Japanese trial compared :
  - Tonsillectomy with steroids
  - Steroids alone
- **Higher proteinuria reduction in the tonsillectomy group but no impact on eGFR over 12 months.**
- In a European cohort, tonsillectomy patients were propensity-score matched to control patients with no benefit in change of GFR or proteinuria.
- **Tonsillectomy may only be considered in IgAN patients with recurrent tonsillitis.**

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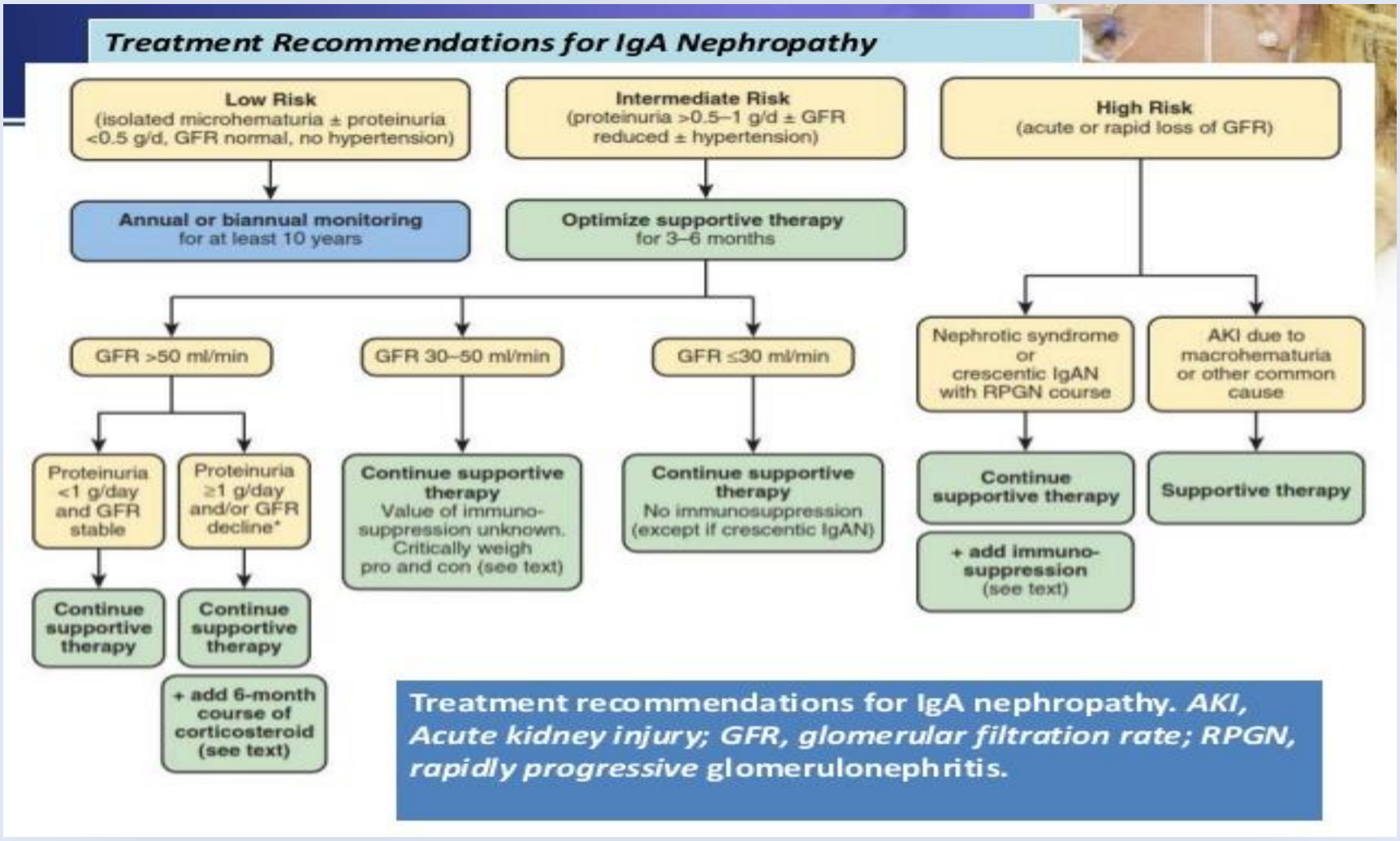
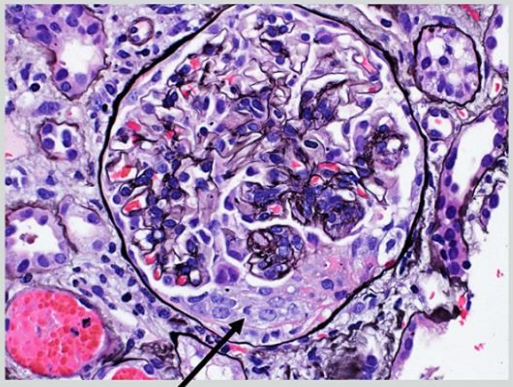
Treatment Recommendations for IgA Nephropathy



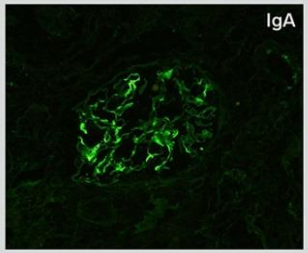
Treatment recommendations for IgA nephropathy. *AKI, Acute kidney injury; GFR, glomerular filtration rate; RPGN, rapidly progressive* glomerulonephritis.

Treatment of IgA Nephropathy, According to KDIGO Guidelines.*
Recommendation ACE inhibitor or ARB for urinary protein excretion of >1 g/day; increase dose depending on blood pressure
Suggestions <u>Proteinuria</u> ACE inhibitor or ARB if urinary protein excretion of 0.5 to 1.0 g/day; increase dose to the extent that adverse events are acceptable to achieve urinary protein excretion of <1 g/day 6-mo glucocorticoid therapy if urinary protein excretion of >1 g/day continues after 3 to 6 mo of proper supportive therapy (ACE inhibitor or ARB and blood-pressure control) and an eGFR of >50ml/min/1.73m2 Fish oil if urinary protein excretion of >1 g/day continues after 3 to 6 mo of proper Supportive therapy
<u>Blood pressure</u>: target is <130/80 mm Hg if urinary protein excretion is <1 g/day but <125/75mm Hg if initial protein excretion is >1 g/day
<u>Rapidly declining eGFR</u> Glucocorticoids and cyclophosphamide for crescentic IgA nephropathy (>50% glomeruli with crescents) with rapid deterioration in eGFR Supportive care if kidney biopsy shows acute tubular injury and intratubular erythrocyte

Crescentic IgA Nephropathy:
KDIGO Definitions and Recommendations for Treatment



Cellular crescent



KDIGO definition of crescentic IgA nephropathy:

– Crescents in greater than 50% of glomeruli **
– Patient has rapidly progressive deterioration in renal function

** New Oxford classification for IgAN identifies two risk groups defined by a 25% crescent cut-off (incorporated in MEST-C score):

C1: <25% crescents – improved renal outcome with immunosuppression
C2: >25% crescents – poor renal outcome despite immunosuppresion

KDIGO recommendations for treatment of crescentic IgA nephropathy:

– Steroids + cyclophosphamide
– Analagous to treatment of ANCA vasculitis

Strength of proposed treatment: "Suggested" (Level 2)

Quality of evidence: "Very low" (Grade D)

KDIGO Clinical practice guideline for glomerulonephritis. Kidney International Supplement Vol. 2, Issue 2, June 2012 p. 215
Trimarchi H, et al. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017 May;91(5):1014-1021. PubMed PMID: 28341274

Arkana Laboratories

Katsumata et al. BMC Nephrology (2018) 19:64
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BMC Nephrology

CASE REPORT Open Access

Successful treatment of recurrent immunoglobulin a nephropathy using steroid pulse therapy plus tonsillectomy 10 years after kidney transplantation: a case presentation

Haruki Katsumata[1*] Izumi Yamamoto[1] Yo Komatsuzaki[1] Mayuko Kawabe[1] Yusuke Okabayashi[1]

Abstract

Background: Both prevention and treatment of recurrent immunoglobulin A nephropathy (IgAN) in kidney transplant recipients are important since recurrent IgAN seems to affect long-term graft survival. We present here a case of recurrent IgAN that was successfully treated using steroid pulse therapy plus tonsillectomy 10 years after kidney transplantation.

Case presentation: A 46-year-old male was admitted for an episode biopsy with a serum creatinine level of 1.8 mg/dl and proteinuria (0.7 g/day). Histological features showed recurrent IgAN (only focal segmental mesangial proliferation) and severe arteriolar hyalinosis partly associated with calcineurin inhibitor toxicity, with limited interstitial fibrosis and tubular atrophy (5%) (IF/TA) 8 years after transplantation. Sodium restriction and conversion from cyclosporine to tacrolimus successfully reduced his proteinuria to the level of 0.15 g/day. However, 2 years later, his proteinuria increased again (1.0 g/day) and a second episode biopsy showed global mesangial proliferation with glomerular endocapillary and extracapillary proliferation accompanied by progressive IF/TA (20%). The steroid pulse therapy plus tonsillectomy successfully decreased his proteinuria and he achieved clinical remission 3 years after this treatment.

Conclusion: This case, presented with a review of relevant literature, demonstrates the difficulty and importance of the treatment of recurrent IgAN and calcineurin inhibitor arteriolopathy, especially in long-term kidney allograft management.

Keywords: IgA nephropathy, Kidney transplantation, Tonsillectomy, Steroid, Calcineurin inhibitor nephrotoxicity, Case report

Observational Study

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Tacrolimus decreases proteinuria in patients with refractory IgA nephropathy

Tingyang Hu, MD, Qingquan Liu, MD, Qing Xu, MD, Hui Liu, MD, Wenhui Qiu, MD, Fei Huang, MD, Shijie Zhang, MD, Yongman Lv, MD*

Abstract

In clinical practice, some IgA nephropathy (IgAN) patients show resistance to or are unable to achieve complete remission using steroids and/or immunosuppressants. The current study aimed to assess the efficacy and safety of tacrolimus in the treatment of cases of refractory IgAN.

In this retrospective observational study, 34 primary IgAN patients with refractory proteinuria received tacrolimus for at least 12 months. Complete remission, partial remission, and other clinical data were measured at 1, 3, 6, and 12 months after the initiation of treatment.

After 12 months, complete remission was achieved in 20 (58.8%) patients and partial remission in 5 (14.7%) patients, yielding a total response rate of 73.5%. The mean time for response to tacrolimus for those who achieved complete remission and partial remission was 7.0 ± 4.7 weeks. Serum creatinine (Scr), uric acid, estimated glomerular filtration rate, alanine aminotransferase, aspartate transaminase, white blood cell count, blood pressure, blood glucose, total cholesterol, and total triglyceride were stable over time. Three patients demonstrated a loss of eGFR > 15 mL/min·1.73 m^2 from baseline. Three cases of upper respiratory infection and 2 cases of urinary tract infection were observed during the study. Patients who achieved complete remission had better renal function and lower baseline proteinuria than partial remission and nonresponder patients. Crescent formation in biopsy specimens was seen more often in nonresponder patients.

Tacrolimus was safe and effective at lowering proteinuria in refractory IgAN patients. Lower baseline proteinuria and better renal function were associated with a higher probability of complete remission, while crescent formation was associated with a worse prognosis.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate transaminase, CYC = cyclophosphamide, IgAN = IgA nephropathy, LEF = leflunomide, MMF = mycophenolate mofetil, Scr = serum creatinine, TC = total cholesterol, TG = total triglyceride, TwHF = *Tripterygium wiforbii* Hook F, UA = uric acid, UACR = urine albumin to creatinine ratio, WBC = white blood cell count.

Keywords: IgA nephropathy, proteinuria, tacrolimus

NEPHROLOGY

Nephrology **23,** Suppl. 4 (2018) 62–67

Review Article

Update on treatment of immunoglobulin A nephropathy

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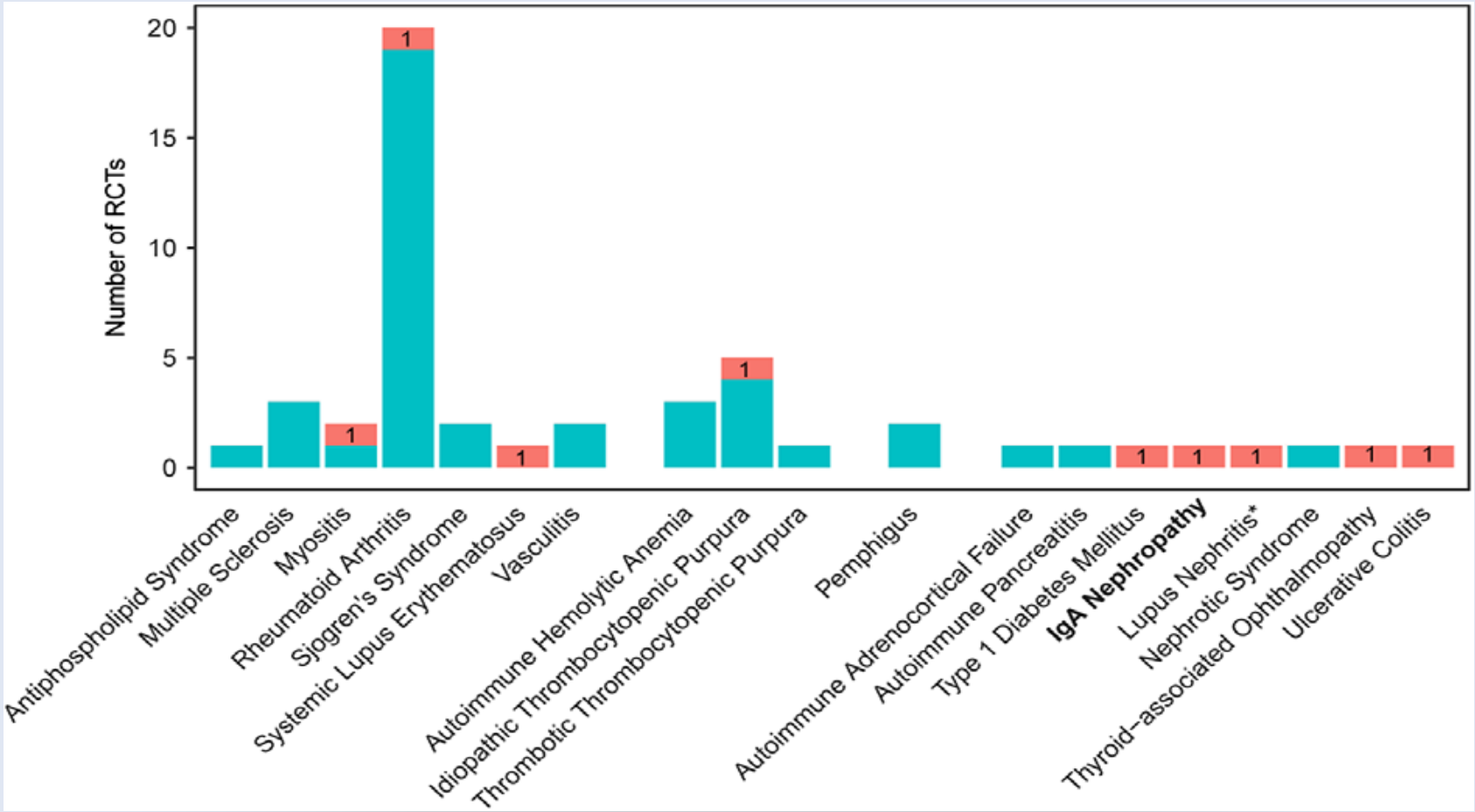
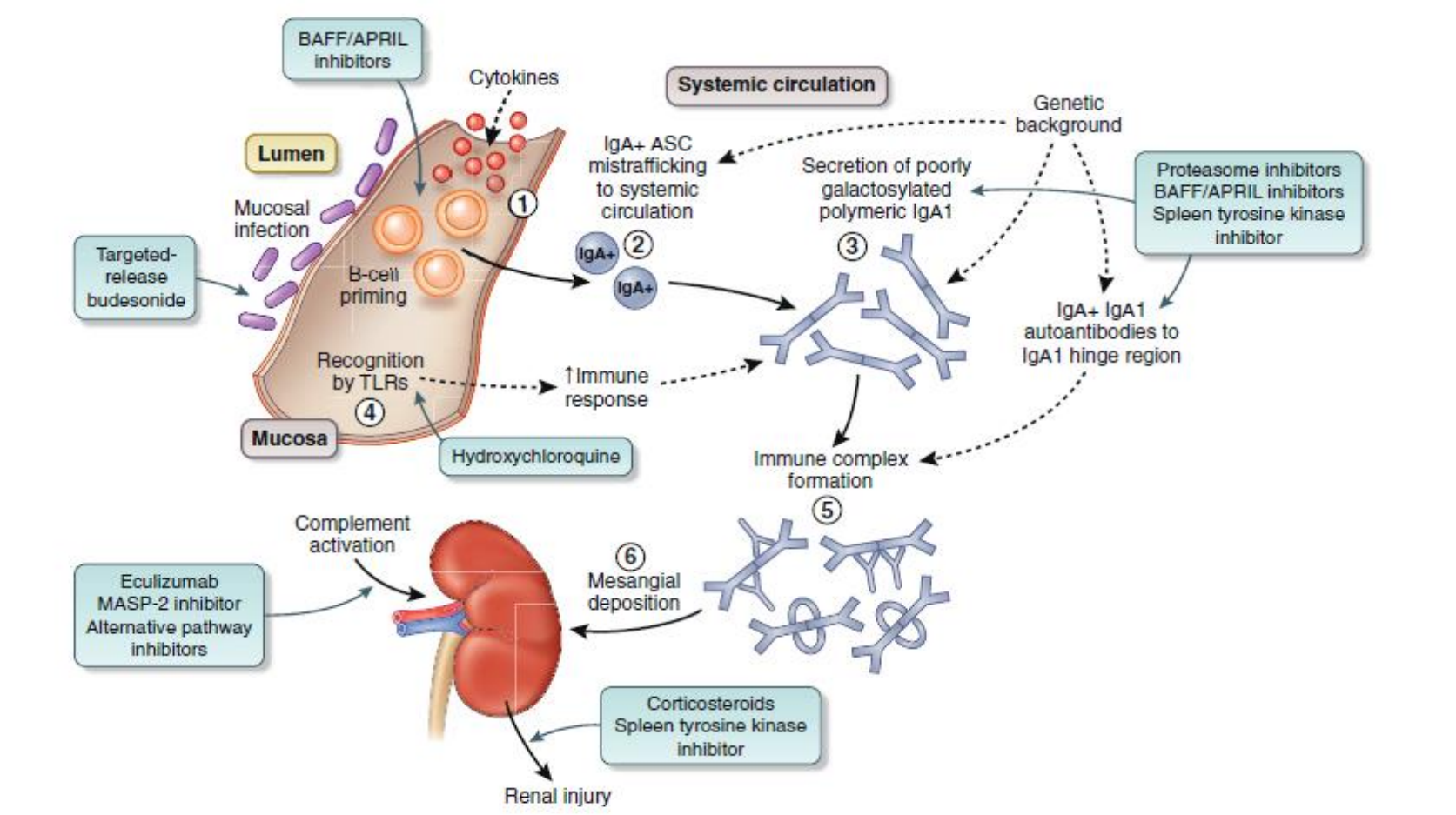


Fig. 2 The efficiency of rituximab in autoimmune diseases. Results of a systematic search on completed randomized controlled trials (RCT) on rituximab through ClinicalTrials.gov (https://clinicaltrials.gov/). (▬) Positive; (▬) negative; IgA, immunoglobulin A.

Proposed pathogenesis of IgA nephropathy (IgAN) and potential therapeutic targets



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Future studies

- Trials of rituximab and tacrolimus have yielded negative results.
- Current trials address the spleen tyrosine kinase inhibitor fostamatinib , and the B-cell activating factor and a proliferation inducing ligand blocker atacicept.
- A pilot study of the proteasome inhibitor bortezomib has just been completed.
- Future multiethnic trials of other pharmacologic agents should incorporate therapeutic drug level monitoring to help determine whether ethnic differences in outcome may be related to pharmacokinetics versus differential disease response.


Thanks for your attention